(c) **Reduction with Sodium and Methanol in Liquid Ammonia.**—Methyl 2,2,6-trimethylcyclohexyl ketimine in liquid ammonia containing methanol was treated with sodium and the reduction product was isolated according to the procedure described above. The ether solution containing the reduction product was washed repeatedly with water, dried with Drierite and evaporated. The liquid residue was dried *in vacuo* over calcium chloride.

Anal. Calcd. for α-methyl-2,2,6-trimethylcyclohexanemethylamine, $C_{11}H_{23}N$: primary amino N, 8.27. Found: primary amino N, 8.31, 7.99.

When tested, this reduction product gave a characteristic isonitrile odor.

The benzenesulfonamide derivative of the reduction product was prepared in 10% sodium hydroxide solution. The solid material which separated was recrystallized twice from 50% aqueous ethanol to yield colorless needles: m. p. 121–122°.

Anal. Calcd. for $C_{17}H_{27}NO_2S$: N, 4.53. Found: N, 4.68.

Reduction of 2,2,6-Trimethylcyclohexanecarbonitrile. (a) Hydrogenation with Adams Catalyst.—2,2,6-Trimethylcyclohexanecarbonitrile was hydrogenated with Adams catalyst and the reduction product and its hydrochloride salt were isolated according to the procedure described above; 156.5 mg. (1.03 millimoles) of the nitrile absorbed 47.4 cc. (2.12 millimoles) of hydrogen.

Anal. Calcd. for 2,2,6-trimethylcyclohexanemethylamine hydrochloride, $C_{10}H_{22}NCl$: primary amino N, 7.31. Found: primary amino N, 7.42, 7.32.

When tested, this reduction product produced an isonitrile odor.

The benzenesulfonamide derivative of the reduction product was prepared in sodium hydroxide solution. The product was recrystallized twice from 50% ethanol, to give colorless needles: m. p. 111–112°.

Anal. Calcd. for $C_{16}H_{25}NO_2S$: N, 4.77. Found: N, 4.74.

Attempts were made to achieve partial hydrogenation of the nitrile by carrying out the hydrogenation in a small volume of methanol containing an excess of concentrated hydrochloric acid. In all cases, the only compounds isolated were the unreacted nitrile and the fully hydrogenated primary amine described above.

(b) **Reduction with Sodium and Methanol in Liquid Ammonia.**—2,2,6 - Trimethylcyclohexanecarbonitrile in liquid ammonia containing methanol was treated with sodium in the manner described above. The benzenesulfonamide derivative of the reduction product was prepared in 10% sodium hydroxide solution: m. p. and mixed m. p. with the benzenesulfonamide derivative of the catalytic reduction product of 2,2,6-trimethylcyclohexanecarbonitrile, 111–112°, indicating that the two methods give the same reduction product, 2,2,6-trimethylcyclohexanemethylamine.

Summary

1. Phenyl 2,2,6-trimethylcyclohexyl ketimine and methyl 2,2,6-trimethylcyclohexyl ketimine have been prepared by treating 2,2,6-trimethylcyclohexanecarbonitrile with phenylmagnesium bromide and methylmagnesium iodide, respectively. These ketimines are not hydrolyzed even on prolonged heating in the presence of concentrated acid or alkali.

2. It appears that these compound possess the ketimine structure because, before reduction, they react like secondary amines to the isonitrile and nitrous acid tests and they yield reduction products which react like primary amines.

3. It is concluded that the abnormal stability of these compounds is due to steric hindrance.

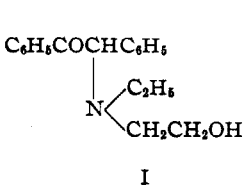
AUSTIN, TEXAS RECEIVED NOVEMBER 17, 1947

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

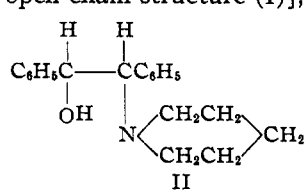
Secondary and Tertiary Amino Ketones and Alcohols Derived from Desoxybenzoin and 1,2-Diphenylethanol.[1] Ring-Chain Tautomerism of the α-(β-Hydroxyethylamino) Ketones[2]

BY ROBERT E. LUTZ, JAMES A. FREEK[3a] AND ROBERT S. MURPHEY[3b]

This investigation was initiated in the fall of 1942 in connection with the search for new types of antimalarials.[2a] The compounds obtained,[4] however, showed no significant activity against avian malaria. At the instigation of Dr. J. L. Hartwell they were then tested at the National Cancer Institute for activity against mammalian tumors, because of their relationship to the nuclear - substituted 1,2 - diphenylethylamines,[5] $ArCH_2CH(NH_2)Ar$, which had already been under investigation as tumor-necrotizing agents. Two of the new compounds when tested in mice gave evidence,[6] at high dosage, of damage to sarcoma 37; these two compounds were α-[N-ethyl-N-(β-hydroxyethyl)-amino]-desoxybenzoin [supposed at the time to have the open-chain structure (I)],



I



II

(1) Agents Causing Necrosis in Tumors. I. This is the first of a series of papers dealing with the search for compounds which may have significance in the hemical treatment of tumors.

(2) (a) The smaller part of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia; (b) the larger part of this work was carried out under a Grant-in-Aid from the National Cancer Institute.

(3) (a) Present location, Department of Pharmacology, University of Virginia Medical School, Charlottesville, Va.; (b) at present holder of a National Cancer Institute Junior Research Fellowship.

(4) These compounds, fourteen in number, which were tested against avian malaria, are listed in the Tables I and II, and are designated by SN numbers which locate them in the "Survey of Antimalarial Drugs, 1941–1945" (by F. Y. Wiselogle, published by J. W. Edwards, 1946).

(5) Hartwell and Kornberg, THIS JOURNAL, **67**, 1606 (1945).

(6) Unpublished work of Shear, Downing, MacCardle, Hartwell, *et al.*, at the National Cancer Institute.

TABLE I

α-(SECONDARY AND TERTIARY-AMINO)-DESOXYBENZOINS OF THE TYPE V AND VIII

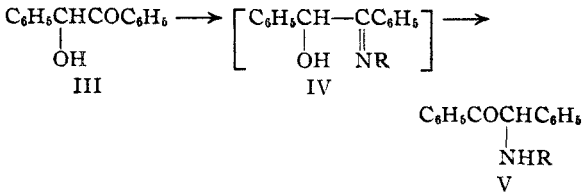
SN[a] or REL[a] no.	NR_2 (base, salt or deriv.)	Prep.[b]	React. time, hr.	Yield, %	Crystallized from[c]	M. p.,[d] °C.	Empirical formula	Analyses,[e,f] Carbon (or N) Calcd.	Carbon (or N) Found	Hydrogen (or Cl⁻) Calcd.	Hydrogen (or Cl⁻) Found
6429	NH(*n*-butyl)·HCl	1a	2	51	Acet.–EtOH	184–186	$C_{18}H_{21}NO\cdot HCl$	71.16	70.90	7.30	7.17[k]
6649	NH(*n*-octyl)·HCl	1a	4	67	Acet.–EtOH	180–182	$C_{22}H_{29}NO\cdot HCl$	73.41	73.12	8.40	8.28[l]
6415	NH(*n*-dodecyl)·HCl	1c	6	55	Acet.–EtOH	153–156	$C_{26}H_{37}NO\cdot HCl$	N, 3.37	3.49	...	....
6648	$NHCH_2C_6H_5\cdot HCl$	1b	4.5	64	Acet.–EtOH	219–222	$C_{21}H_{19}NO\cdot HCl$	N, 4.15	3.94	...	....
6328	$NHCH_2CH_2C_6H_5\cdot HCl$	1b	4.5	72	Acet.–EtOH	230–232	$C_{22}H_{21}NO\cdot HCl$	N, 3.98	4.22	...	....
617[a]	$NHCH_2CH_2OH\cdot HCl$	1d	3	20[j]	*i*-PrOH–H_2O[i]	188–189	$C_{16}H_{17}NO_2\cdot HCl$	65.86	65.83	6.22	6.30
639[a]	$NHCH_2CH(OH)CH_3\cdot HCl$	1d	10	6[j]	Ethanol	173–174.5	$C_{17}H_{19}NO_2\cdot HCl$	66.77	66.76	6.59	6.50
..	$NHC_6H_4(C_2H_5)_2(p)$	..	..	..	60% EtOH	72– 74	$C_{24}H_{28}N_2O$	N, 7.82	7.67	...	....
612[a]	(hydrochloride)	1a	2	97	EtOH–H_2O	208–209	$C_{24}H_{26}N_2O\cdot HCl$	72.98	73.17	6.89	7.08
..	Piperidyl[10a]	..[g]	..	..	Ethanol	82– 83	.....	...	..	...	....
3636	(hydrochloride)	2[g]	..	..	EtOH–Ether	225–227[h]	$C_{19}H_{21}NO\cdot HCl$	N, 4.44	4.29	Cl, 11.23	11.37
3634	$N(C_2H_5)CH_2CH_2OH$	..	..	..	Ethanol	96– 97	$C_{18}H_{21}NO_2$	76.29	76.60	7.47	7.25
..	(hydrochloride)	2	3	43	EtOH–ligr.	204–205	$C_{18}H_{21}NO_2\cdot HCl$	67.59	67.39	6.93	6.67[m]
3101	N(*n*-butyl)CH_2CH_2OH	2	2.5	24	Ligroin	75– 76.5	$C_{20}H_{25}NO_2$	N, 4.50	4.75	...	....
..	(hydrochloride)	..	..	..	.....	159–161.5	$C_{20}H_{26}NO_2\cdot HCl$	71.15	71.02	7.30	7.18[n]
643[a]	$N(CH_2CH_2OH)_2$	2	4	44	Ethanol	135–136	$C_{18}H_{21}NO_3$	72.21	73.31	7.07	7.14[p]
..	(hydrochloride)	..	..	..	.....	190–191	$C_{18}H_{21}NO_3\cdot HCl$	71.15	71.02	7.30	7.18

[a] The three-digit numbers are code numbers from this Laboratory. [b] Preparative methods A, B and C, are described in the experimental part, together with notes dealing with variations in the procedures and manipulations involved. [c] Acet. = acetone; *i*-PrOH = isopropanol; EtOH = 95% ethanol, or absolute ethanol where used with other solvents; ligr. = ligroin. [d] All melting points are "corrected." [e] Extra analyses: see footnotes *k* to *p*. [f] N = analysis for nitrogen. Cl = analysis for chloride ion by Mohr titration. [g] See experimental part. [h] Melts with decomposition. [i] With a little ether added. [j] In some cases where the yields listed are low, enough material was obtained in the preliminary experiments for testing, and no attempts were made in those cases to repeat the experiments because of the lack of time. [k] Calcd. for N, 4.61; Cl, 11.67. Found: N, 4.62; Cl, 11.88. [l] Calcd. for N, 3.89; Cl, 9.85. Found: N, 4.29; Cl, 9.84. [m] Calcd. for N, 4.38; Cl, 11.08. Found: N, 4.48; Cl, 11.18. [n] Calcd. for N, 4.03. Found: 4.11. [p] Calcd. for N, 4.68. Found: 5.11.

and the related 1,2-diphenyl-2-N-piperidylethanol (II).

Because of these findings the synthetic work in this series was extended. The results are summarized in Tables I and II where the various mono- and disubstituted-amino ketones and alcohols are listed.[7] The discussion of new chemistry incidental to the preparation of these compounds follows. The pharmacological results will be reported elsewhere.[6]

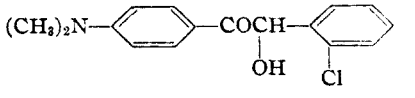
The Reaction between Benzoin and Primary Aliphatic Amines.—This condensation was used to prepare a series of seven monoalkylamino and the *p*-diethylaminoanilino ketones (V).



It was adapted from the Voigt reaction[8] which up to this time had been applied only to aromatic amines. One attempt had been made to use an aliphatic amine in this reaction,[8b] but it was unsuccessful, perhaps because no catalyst was employed. In the present work phosphorus pentoxide or hydrochloric acid was used as the condensing agent and the reaction appeared to be general and proceeded with good yields.

Two aliphatic N-monoalkylamino desoxybenzoins have already been made in small yields by the palladium-catalyzed hydrogenation of benzil in the presence of cyclohexylamine and 3-aminopentane.[9] The first of these (V, R = cyclohexyl) has now been made in a second way by the Voigt reaction.

Some observations in the present work are pertinent to the mechanism proposed for the Voigt reaction, which involves first the formation of the Schiff base of benzoin (IV) followed by rearrangement to the monoarylamino ketone.[8c,d,e] The highly branched-chain amines, tris-(hydroxymethyl)-methylamine and 2-amino-1,3-dihydroxymethyl-2-methylpropane, do not undergo the reaction under the conditions applicable to ordinary primary amines, presumably because of steric interference with addition at the carbonyl groups.



VI

Furthermore 2′-chloro-4-dimethylaminobenzoin does not undergo this reaction with *n*-butyl and *n*-octylamines under the usual conditions, presumably also because of lowered activity of the carbonyl group, lowered in this case chemically by the *p*-dimethylamino group.

The monoalkylamino ketones are unstable in the form of the free bases and only the hydrochlorides have been isolated. In many cases it was observed that the bases underwent facile

(7) *Cf.* also Lutz and Murphey, the 4,4′-dichloro series, a paper to be published shortly.

(8) (a) Voigt, *J. prakt. Chem.*, [2] **34**, 2 (1886); (b) *cf.* also Cameron, Nixon and Basterfield, *Trans. Roy. Soc. Can.*, **3**, 25, Sect. 3, 145 (1931); (c) Cowper and Stevens, *J. Chem. Soc.*, 374 (1940); *cf.* also (d) Strain, THIS JOURNAL, **51**, 269 (1929); (e) Julian, Meyer, Magnani and Cole, *ibid.*, **67**, 1203 (1945).

(9) Skita and Keil, *Ber.*, **66**, 858 (1933).

TABLE II

2-(SECONDARY AND TERTIARY-AMINO)-1,2-DIPHENYLETHANOLS OF THE TYPE IX

REL[a] or SN[a] no.	NR₂ (base or deriv.)	Prep. method[c]	Time heating, hrs.	Yield, %	Crystallized from[d]	M. p., °C. (cor.)	Empirical formula	Analyses/ Carbon (or N) Calcd.	Found	Hydrogen (or Cl⁻) Calcd.	Found
..	NH_2[15,16,17,18]	2a[k]	10	92	EtOH	165–166	$C_{14}H_{15}NO$	N, 6.57	6.54	...	....
677[a]	(hydrochloride)	...	..	..	CH_3OH	233–234	$C_{14}H_{15}NO\cdot HCl$	N, 5.61	5.41	...	....
..	NH_2[b,15,16,17]	2a[k]	6	92	EtOH	127–128	$C_{14}H_{15}NO$	N, 6.57	6.49	...	....
673[a]	(hydrochloride)[b]	...	..	..	CH_3OH	209–211	$Base\cdot HCl\cdot CH_3OH$	N, 4.97	5.16	...	....
..	NH(*n*-butyl)	1a	7	26	EtOH	135–136.5	$C_{18}H_{23}NO$	80.25	80.18	8.61	8.62
		2a[h]	8	44	EtOH	134–135	$C_{18}H_{23}NO$	N, 5.20	5.22	...	....
6413	(hydrochloride)	1a	..	..	.....	215–216	$C_{18}H_{23}NO\cdot HCl$	...	...	Cl, 11.60	11.76
..	(picrate)	...	..	..	Dil.EtOH	154.5–155	$Base\cdot C_6H_3N_3O_7$	57.82	57.96	5.46	5.60
..	NH(*n*-butyl)[b]	2a	18	83	90% EtOH	63– 64	$C_{18}H_{23}NO$	80.25	80.51	8.61	8.79[n]
633[a]	(hydrochloride)[b]	2a	..	..	Acetone	181–182	$C_{18}H_{23}NO\cdot HCl$	N, 4.58	4.37	...	....
..	(picrate)[b]	...	..	..	Dil.EtOH	176–177.5	$Base\cdot C_6H_3N_3O_7$	57.82	57.33	5.46	5.47
..	NH(2-heptyl)	2b	3.5	59	EtOH	97– 99	$C_{21}H_{29}NO$	N, 4.50	4.27	...	....
653[a]	(hydrochloride)	2b	..	..	Lig.–But.	138–140	$C_{21}H_{29}NO\cdot HCl$	72.49	72.38	8.69	8.64[p]
..	NH(*n*-octyl)	2b	0.5	85	EtOH	120–121	$C_{22}H_{31}NO$	81.18	80.88	9.60	9.67[q]
654[a]	(hydrochloride)	2b	..	..	But.–CH_3OH	193–194	$C_{22}H_{31}NO\cdot HCl$	N, 3.87	3.61	...	....
..	NH(*n*-dodecyl)	1a	11	56	Acetone	112–115	$C_{26}H_{39}NO$	81.84	81.52	10.30	10.33[r]
		2b[h]	7.5	48	Acetone	112–114	$C_{26}H_{39}NO$	N, 3.67	3.71	...	....
6426	(hydrochloride)	1a	..	..	Acet.–EtOH	145.5–148	$C_{26}H_{39}NO\cdot HCl$	...	...	Cl, 8.48	8.52
..	NH(cyclohexyl)[g]	3	..	71	Benz.–EtOH	163–164	$C_{20}H_{29}NO$	...	..	...	....
		2a[h]	1.5	76	EtOH	163–164	$C_{20}H_{29}NO$	N, 4.74	4.69	...	....
681[a]	(hydrochloride)	...	..	..	EtOH	239–240[j]	$C_{20}H_{29}NO\cdot HCl$	72.38	72.42	7.90	8.16
..	NH(cyclohexyl)[b]	2a	2	62	Dil.EtOH	71– 73	$C_{20}H_{29}NO$	N, 4.74	4.85	...	....
657[a]	(hydrochloride)[b]	...	..	..	But.–CH_3OH	251–252	$C_{20}H_{29}NO\cdot HCl$	N, 4.22	4.50	...	....
6427	$NHCH_2C_6H_5$[14]	1a[e]	24	38	Acet.–EtOH	154–155.5	$C_{21}H_{21}NO$	N, 4.62	4.38	...	....
		2b[h]	2	83	But.–EtOH	154–155	$C_{21}H_{21}NO$	N, 4.62	4.33	...	....
..	(hydrochloride)	...	..	..	.....	228–229	$C_{21}H_{21}NO\cdot HCl$	...	...	Cl, 10.43	10.60
..	(dibenzoate)	...	..	..	EtOH	166–167.5	$C_{35}H_{29}NO_3$	N, 2.74	2.78	...	....
..	$NHCH_2CH_2C_6H_5$	1a	24[i]	41	Acet.–EtOH	154–155	$C_{22}H_{23}NO$	N, 4.41	4.11	...	....
		b[h]	10	69	.....	153–154	$C_{22}H_{23}NO$	N, 4.41	4.54	...	....
6653	(hydrochloride)	...	..	..	EtOH	245–246	$C_{22}H_{23}NO\cdot HCl$	...	..	Cl, 10.02	10.16
634[a]	$NHCH_2CH_2OH$	2b	2	48	Benzene	105–105.5	$C_{16}H_{19}NO_2$	74.68	74.90	7.44	7.56
..	(hydrochloride)	1a	8	83	Acet.–Ether	237–238.5	$C_{16}H_{19}NO_2\cdot HCl$	N, 4.77	5.10	...	....
..	$NHCH_2CH_2CH_2N(C_2H_5)_2$	1a	2	61	Ligroin	136–137	$C_{21}H_{30}N_2O$	77.25	76.92	9.26	8.85[s]
271[a]	(dihydrochloride)	...	..	..	.....	228–229	$C_{21}H_{30}N_2O\cdot 2HCl$	N, 7.38	7.16	...	....
..	$NHC_6H_4(C_2H_5)_2(p)$	1b	3.5	99	70% EtOH	108–109.5	$C_{24}H_{28}N_2O$	N, 7.78	7.62	...	....
618[a]	(dihydrochloride)	...	..	..	But.–CH_3OH	202–202.5	$C_{24}H_{28}N_2O\cdot 2HCl$	66.50	66.21	6.98	7.05
..	$N(Ethyl)_2$	2a	12	17	Dil.EtOH	71– 72	$C_{18}H_{23}NO$	N, 5.20	5.22	...	....
661[a]	(hydrochloride)	...	..	..	But.–CH_3OH	218–219	$C_{18}H_{23}NO\cdot HCl$	N, 4.58	4.62	...	....
..	$N(butyl)_2$	2c	11	22	Dil.EtOH	45– 46	$C_{22}H_{31}NO$	N, 4.30	4.26	...	....
656[a]	(hydrochloride)	...	..	..	But.–CH_3OH	146–148	$C_{22}H_{31}NO\cdot HCl$	N, 3.87	4.03	...	....
..	Piperidyl	1	6.5	26	EtOH	109–110	$C_{19}H_{21}NO$	81.10	81.15	8.24	8.26
		2a[h]	12	84	EtOH	109–110	$C_{19}H_{21}NO$	N, 4.98	5.17	...	....
6423	(hydrochloride)	...	..	..	EtOH	259–260[l]	$C_{19}H_{21}NO\cdot HCl$	71.80	71.67	7.61	7.56
..	(benzoyl deriv.)	...	..	..	EtOH	166.5–167	$C_{26}H_{27}NO_2$	81.00	80.74	7.06	7.19
..	(methiodide)	...	..	..	H_2O	227–228.5	$C_{20}H_{26}INO$	56.74	56.74	6.19	6.32
..	Piperidyl[b]	1	6.5	25	EtOH	101–102[g]	$C_{19}H_{21}NO$	81.10	80.86	8.24	8.23
		2a[h]	8	63	EtOH	101–102	$C_{19}H_{21}NO$	N, 4.98	5.16	...	....
620[a]	(hydrochloride)[b]	...	..	..	EtOH	202–203	$C_{19}H_{21}NO\cdot HCl$	N, 4.41	4.32	...	....
..	(benzoyl deriv.)[b]	...	..	..	EtOH	143–144	$C_{26}H_{27}NO_2$	81.01	81.22	7.06	6.84
..	2-Methylpiperidyl	2a	12	79	EtOH	107–108	$C_{20}H_{23}NO$	81.31	81.41	8.53	8.24[t]
649[a]	(hydrochloride)	...	..	..	But.–CH_3OH	204–206	$C_{20}H_{23}NO\cdot HCl$	N, 4.22	3.99	...	....
..	3-Methylpiperidyl	2	12	67	EtOH	91– 93	$C_{20}H_{23}NO$	N, 4.74	4.98	...	....
648[a]	(hydrochloride)	...	..	..	But.–CH_3OH	217–219	$C_{20}H_{23}NO\cdot HCl$	N, 4.22	4.12	...	....
..	4-Methylpiperidyl	2	4	84	EtOH	112–113.5	$C_{20}H_{23}NO$	81.31	81.24	8.53	8.41[u]
645[a]	(hydrochloride)	...	..	..	But.–CH_3OH	245–246	$C_{20}H_{23}NO\cdot HCl$	N, 4.22	4.15	...	....
..	2-Hexylpiperidyl	2c	18	20	Dil.EtOH	47– 48	$C_{23}H_{33}NO$	N, 3.83	4.08	...	....
658[a]	(hydrochloride)	...	..	..	Acet.–ligr.	181–182	$C_{23}H_{33}NO\cdot HCl$	N, 3.48	3.63	...	....
..	2,4-Dimethylpiperidyl	2c	4	47	.....	Oil	.....	...	...	...	....
646[a]	(hydrochloride)	...	..	..	But.–CH_3OH	274–249	$C_{21}H_{27}NO\cdot HCl$	72.92	72.64	8.16	8.20[v]
..	Tetrahydroisoquinolyl	2c	1	43	EtOH	99–100	$C_{24}H_{23}NO$	N, 4.25	4.02	...	....
655[a]	(hydrochloride)	...	..	..	But.–CH_3OH	223–225	$C_{24}H_{23}NO\cdot HCl$	75.50	75.23	6.61	6.62[w]
635[a]	$N(C_2H_5)CH_2CH_2OH$	...	..	..	EtOH	80– 81	$C_{18}H_{23}NO_2$	N ,4.91	4.81	...	....
..	(hydrochloride)	2a	12	47.5	But.–EtOH	183–184	$C_{18}H_{23}NO_2\cdot HCl$	67.17	66.91	7.52	7.64
6422	Morpholinyl·HCl	1b	..	..	EtOH	155–157	$C_{18}H_{21}NO_2\cdot HCl$	N, 4.38	4.24	...	....

[a] Three-digit numbers are code numbers from this laboratory. [b] These are the B-stereoisomers which are made from *cis*-stilbene oxide and where the configuration is considered to be "threo." [c] Referring to preparative methods 1 and 2 which are described in the experimental part. [d] But. = butanone; Acet. = acetone; Benz. = benzene. [e] We were unable to obtain a "benzoyl" derivative of the melting point reported.[14] However, this dibenzoyl derivative melted at the point reported[14] at one stage of the purification. [f] N = analysis for nitrogen. Cl = analysis for chloride ion by Mohr titration. [g] A mixture melting point with the A-isomer showed a significant depression. [h] The two samples made by the two different methods were identified by mixture melting points. [i] Time of heating, ten hours. [j] Melting point reported

by Skita and Keil,[o] 264–265°. [k] See experimental part. [l] *In vacuo*. [m] Methanol of crystallization. Additional analyses: [n] Calcd. for N, 5.20; found, 5.16. [p] Calcd. for N, 4.03; found, 3.99. [q] Calcd. for N, 4.30; found, 4.24. [r] Calcd. for N, 3.67; found, 3.69. [s] Calcd. for N, 8.58; found, 8.42. [t] Calcd. for N, 4.74; found, 4.85. [u] Calcd. for N, 4.74; found, 4.78. [v] Calcd. for N, 4.05; found, 4.10. [w] Calcd. for N, 3.83; found, 3.84.

hydrolysis and oxidation during preparation of the hydrochlorides with the resulting formation of the primary amine and benzil. This secondary reaction often caused considerable loss in yield during purifications. The interesting question as to whether this formation of benzil was due to initial oxidation of the amino ketone to the mono-Schiff base of benzil followed by hydrolysis, or to hydrolysis to benzoin followed by oxidation (or to both of these as competing reactions) has not been answered. It is noteworthy, however, that in one case the γ-diethylaminopropylamino ketone [V, R = $NHCH_2CH_2CH_2N(C_2H_5)_2$, obtained as an oil and not characterized, but successfully reduced nevertheless to the diamino alcohol] was hydrolyzed readily by moist ethereal hydrogen chloride to benzoin.

Condensation of Desyl Chloride with Secondary Amines.—Three new dialkylamino desoxybenzoins (VIII) have been made by this method, and also α-piperidyldesoxybenzoin (VIII, NR_2 = piperidyl) which had previously been made by the action of N-chloropiperidine on desoxybenzoin.[10]

$$\underset{\text{VII}}{C_6H_5COCHC_6H_5} \xrightarrow{NHR_2} \underset{\text{VIII}}{C_6H_5COCHC_6H_5}$$
(Cl) (NR₂)

The Preparation of β-Mono and Dialkylamino Alcohols by Reductions.—Reductions of the mono- and dialkylaminodesoxybenzoins were accomplished by means of aluminum isopropoxide. In all but one case moderate yields of only one of the two possible diastereoisomeric amino alcohols were obtained. Doubtless the

$$\underset{\text{IX}}{C_6H_5CH(OH)—CH(NR_2)C_6H_5}$$

other diastereoisomers were also formed in many of these reductions but escaped detection because they were the minor and the more soluble forms.

The probabilities are that the amino alcohols obtained as the chief products from these reductions, are of the same type-configuration (arbitrarily designated as type-A) because in each of five cases, namely, the butyl, cyclohexyl, dodecyl, benzyl and phenylethylamino, these same compounds were isolated as the sole products, respectively, when *trans* stilbene oxide was condensed with the appropriate amines, and because in two cases studied, namely, the butyl and cyclohexylamino, the stereoisomeric lower-melting amino alcohols were obtained as the sole products, respectively, of the condensations with *cis* stilbene oxide.

(10) (a) Rabe, *Ber.*, **45**, 2169 (1912); (b) for the α-(N-morpholinyl)-desoxybenzoin (SN 2594), see *C. A.*, **33**, 6527 (1939) [German Patent 671,786].

Although the platinum-catalyzed reduction of α-piperidyldesoxybenzoin hydrochloride gave chiefly the one stereoisomer-A and appears to be consistent stereochemically with the other reductions described above, the reduction of either the base or the hydrochloride by means of aluminum isopropoxide gave difficultly separable mixtures of the two diastereoisomers. This constitutes the only case in the 1,2-diphenyl series where the B-type stereoisomer has actually been isolated as a reduction product, and the result is to be compared with the reduction of the amino ketone $C_6H_5COCH(CH_3)NHCH_3$ to ephedrine where, however, only a relatively smaller amount of the stereoisomer is formed.[11]

The second and lower-melting stereoisomeric piperidyl alcohol was subsequently obtained as the sole product of condensation of *cis*-stilbene oxide with piperidine.

The methylamino and cyclohexylamino alcohols, which are described in the literature, were made in a second way by platinum-catalyzed hydrogenation of a mixture of benzil and the primary amine.[12] It has been suggested that this reaction proceeds through the monoalkimine (X). It is

$$\underset{\text{X}}{C_6H_5COC(=NR)C_6H_5}$$

conceivable however that reduction of benzil to benzoin occurs first, and that this is followed by the formation of the benzoin-alkimine (IV) and/or the alkylamino ketone (the Voigt reaction) and reduction to the alkylamino alcohol. This alternative mechanism is suggested by the fact that the acyloin, $C_6H_5CHOHCOCH_3$, undergoes reductive amination to ephedrine,[13] and it has been tested as follows. The platinum-catalyzed hydrogenation of a mixture of benzil and cyclohexylamine (analogously to Skita's experiment[12a]) gave a cyclohexylamino alcohol corresponding in properties and evidently identical with that obtained by Skita. The product was shown to be of the type-A configuration by synthesis also from *trans*-stilbene oxide. Repetition of this hydrogenation experiment using benzoin in place of benzil, however, produced only *meso* hydrobenzoin in nearly quantitative yield. Therefore benzoin and the Voigt reaction could not have been involved here.

The Preparation of β-Mono and Dialkylamino Alcohols by Condensation of the Stilbene Oxides with Primary and Secondary Amines.—Of the compounds listed in Table II, ten sec-

(11) Manske and Johnson, THIS JOURNAL, **51**, 580 (1929).

(12) (a) Skita and Keil, *Ber.*, **62**, 1142 (1929); *C. A.*, **24**, 1119 (1930) [British Patent 313,617 (1928)]; the 4,4'-dimethoxy-N-methyl analog was made also.

(13) Hildebrandt and Klavehn, *C. A.*, **26**, 3623 (1932) [German Patent 548,459 (1930)]; *C. A.*, **28**, 4072 (1934) [U. S. Patent 1,956,950 (1934)].

ondary-amino and eleven tertiary-amino alcohols (*cf.* IX) have been made by condensation of *trans* stilbene oxide (XI) with appropriate amines. Because five of these compounds were identical with the products of reduction of the substituted-amino ketones, all of these compounds which clearly belong to the same stereochemical system are classified as type-A. The five stereoisomeric secondary- and tertiary-amino alcohols made similarly from *cis*-stilbene oxide (XII) have been designated configurationally as type-B.

It is noteworthy that *trans*-stilbene oxide was successfully condensed with three typical 2-substituted piperidines (the 2-methyl, 2-hexyl and 2,4-dimethyl), but that 2,4,6-trimethylpiperidine did not undergo this condensation, presumably because of excessive steric hindrance at the nitrogen.

Incidentally it should be mentioned at this point that the various condensations of β-ethanolamine with the stilbene oxides have been shown actually to involve the NH-group rather than the hydroxyl, as would be expected. The evidence is the fact that in one case the resulting β-(β-ethanolamino) alcohol (IX, NR_2 = $NHCH_2CH_2OH$) is obtainable in a second way by reduction of the α-(β-ethanolamino) ketone (V, NHR = $NHCH_2CH_2OH$) the structure of which is certain from the mode of synthesis from benzoin by the Voigt condensation with ethanolamine.

All of the secondary amino alcohols listed in Table II are new except the two with indicated references. One of these, the benzylamino compound, was first made by a complex reaction from benzaldehyde through the action of sodium nitrite, formic or acetic acid and zinc.[14] The properties reported for this compound, both the free base and the hydrochloride, agree with those of the samples we have prepared from *trans*-stilbene oxide. The configuration therefore appears to correspond to type-A.

For the purpose of comparative tests the two aminohydrins (known[15]) (IX, NR_2 = NH_2) were made in a new way by the ammonolysis of the *trans* and *cis* stilbene oxides. The higher-melting isomer (m. p. 165–166°) obtained from the *trans* oxide, is the one obtained by hydrolysis of the *trans* imine,[16] and is the one obtained in the reductions of aminodesoxybenzoin,[17] the benzilmonoximes[17] and benzoin oxime[18]; it evidently corresponds in configuration to the type-A. The lower-melting isomer (m. p. 127–128°) obtained from the *cis* oxide, is the one obtained by hydrolysis of the *cis* imine[16] and corresponds therefore to type-B. Thus the stereochemical picture here corresponds exactly to that described above for the mono and dialkylamino alcohols.

(14) Ogato and Hirano, *J. Pharm. Soc. Japan*, **50**, 1141 (1930) [*C. A.*, **25**, 1819 (1931)].

(15) McKenzie and Pirie, *Ber.*, **69**, 876 (1936).

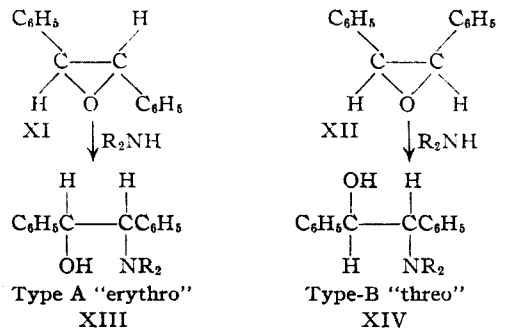
(16) Weissberger and Bach, *ibid.*, **65**, 631 (1932).

(17) Polonowska, *ibid.*, **21**, 488 (1888); Erlenmeyer, *ibid.*, **29**, 295 (1896).

(18) Söderbaum, *ibid.*, **28**, 2523 (1895); Erlenmeyer, *ibid.*, **30**, 1525 (1897); Polonowska, *ibid.*, **20**, 493 (1887).

The Assignment of Relative and Specific Configurations to the Amino Alcohols.—The condensations between primary, secondary amines and ammonia, and the *cis* and *trans* stilbene oxides (XI and XII) have proceeded consistently in each case in only one of the two possible stereochemical senses, and in this respect they are comparable with three types of stereochemically consistent reactions (a) the hydrochlorination of the stilbene oxides,[19] (b) the formation of the stilbene oxides from the halohydrins[19] and aminohydrins,[20] and (c) the hydrolysis of the *cis* and *trans* imines.[16] The normal or chief p oducts of reductions in which the two-asymmetric-carbon system is generated correspond in so far as has been tested, to the compounds obtained from the *trans* oxide; and the two synthetic methods therefore serve as independent means of assignment of type-configurations. However, because in one isolated case in this investigation a reduction actually did give simultaneously both of the two possible stereoisomeric products, the synthesis from the stilbene oxides where no such exception has appeared, is clearly the more reliable and is the preferred basis for stereochemical classification. Those compounds obtained in reductions which have not been directly or indirectly related by synthesis to the stilbene oxides are to be regarded as probably of the type-A configuration, and the assignment of configurations in these cases is tentative.

The specific configurations of these products have been assigned tentatively (a) on the assumption that the oxide ring-opening is consistently *trans* as has been demonstrated in the hydrochlorination and hydrolysis[21] of maleic and fumaric acid oxides, and (b) on the basis of analogy to the consistent stereochemical mode of reductions, namely, the catalytic, sodium amalgam or aluminum isopropoxide reductions[22] of benzoin which give chiefly the *meso* hydrobenzoin, and the reduction of benzil dioxime predominantly to *meso*



(19) (a) Reulos, *Compt. rend.*, **216**, 774 (1943); (b) Reulos and Collin, *C. A.*, **40**, 3743 (1946) [*Compt. rend.*, **218**, 795 (1944)].

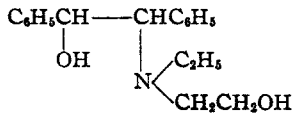
(20) Reid and Campbell, *J. Chem. Soc.*, 2377 (1930).

(21) (a) Kuhn and Zell, *Ber.*, **59**, 2514 (1926); (b) Kuhn and Wagner-Jaureg g, *ibid.*, **61**, 504 (1928).

(22) (a) See experimental part; (b) Irvine and Weir, *J. Chem. Soc.*, **91**, 1390 (1907); (c) Breuer and Zincke, *Ann.*, **198**, 141 (1879); (d) Lund, *Ber.*, **70**, 1520 (1937); (e) Hayashi, *C. A.*, **41**, 6561 (1947) [*Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **39**, 107 (1941)].

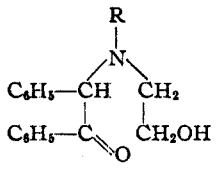
stilbenediamine.[22e] Thus the type-A compounds are presumed to be "erythro" as formulated (XIII) and the type-B compounds are tentatively formulated as "threo" (XIV).

Ring-Chain Tautomerism of the α-(β-Hydroxyethylamino)-desoxybenzoins.—One negative result in the earlier aluminum isopropoxide reductions of the various substituted-amino desoxybenzoins stood out as striking; the reductions had proceeded effectively in all cases except one, namely, α-[N-ethyl-N-(β-ethanol)-amino]-desoxybenzoin (I). This compound either as the base or as the hydrochloride was recovered unchanged after prolonged treatment, yet the corresponding ethylethanolamino alcohol (XV), could easily be made through condensation of *trans*-stilbene oxide with ethylethanolamine.

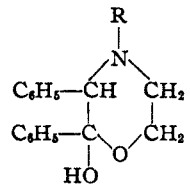


XV ("erythro")

It was of significance that this exceptional compound was the only one of the group of compounds reduced up to that time, which carried a β-hydroxyethyl group on the nitrogen. The unexpected resistance to reduction by the carbonyl-specific reagent, aluminum isopropoxide, suggested that the compound exists in the tautomeric ring form, XVIBa.



XVIA



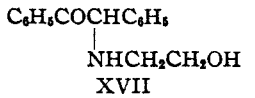
XVIB

(a) R = C_2H_5
(b) R = *n*-butyl
(c) R = CH_2CH_2OH

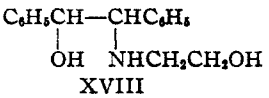
The ability of compounds of this type to function in the tautomeric cyclic sense is already implied in the conversion of one N-benzoyl compound of this type into a dehydromorpholine (dihydro-1,4-oxazine)[23] under the action of alcoholic hydrogen chloride. However, the present results indicate more than this, namely, that the cyclic hemiacetal form of these compounds actually can exist and in some cases is the stable tautomer. This phenomenon, of ring-chain tautomerism, if it has been correctly interpreted, might have been predicated from the probable influence of the α-amine nitrogen atom on the carbonyl group, an influence which should be to some extent analogous to that exerted by the δ-hydroxyl group in the ketone sugars and related compounds where the cyclic structures are the stable ones.

(23) (a) Hill and Powell, THIS JOURNAL, **67**, 1462 (1945); *cf.* also (b) Knorr, *Ber.*, **32**, 729 (1898); (c) Wolff and Marburg, *Ann.*, **368** 169 (1908); (d) Coghill, THIS JOURNAL, **59**, 801 (1937).

In order to explore the β-hydroxyethylamino ketones further in respect to reducibility by aluminum isopropoxide, three other compounds of the type were made. The β-hydroxyethylamino compound itself (XVII) in which the nitrogen is secondary, was reduced, with normal ease, to the dihydroxyamine (XVIII), whereas the tertiary



XVII

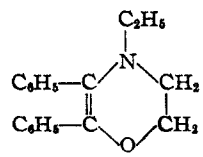


XVIII

N-butyl-N-(β-hydroxyethyl)-amino and di-(β-hydroxyethyl)-amino compounds (XVIBb and c) failed to undergo reduction. It is to be concluded from this that the latter two compounds which carry tertiary nitrogens are cyclic under these conditions like the ethylethanolamino compound (XVIBa), but that the monoethanolamino compound itself, which is secondary with respect to the nitrogen, either is open-chain (XVII) or involves a relatively labile ring-chain tautomerism. It thus seems that cyclization or stability of the cyclic tautomer is favored by N-substituents.

There are, of course, other though unlikely interpretations of these failures of aluminum isopropoxide reductions; for example, some special or peculiar influence of the hydroxyl group located β to the nitrogen and δ to the carbonyl, through chelation, hydrogen-bonding or aluminum-complex formation, perhaps through enolization. However, it should be stressed that many and various of the ordinary N-substituted secondary and tertiary desylamines (of the type V and VIII) have now been made and have been reduced successfully by means of aluminum isopropoxide, and that a close analog which is not represented in Tables I and II, the N,N-diethyl, has been made in the 4,4′-dichlorodesoxybenzoin series and has proved to be readily reducible in this same way.[7] Furthermore the simple monoethanolamino ketone (XVII) is readily reducible by aluminum isopropoxide. In view of these facts, no influence other than ring-chain tautomerism is apparent which might account for the diminished reactivity of these compounds toward aluminum isopropoxide.

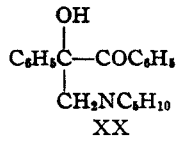
As a consequence of this phenomenon of ring-chain tautomerism it was anticipated that dehydration of the ethanolamino ketones could be accomplished easily (*cf.* ref. 23) by heating these compounds above their melting points. β-(Ethylethanolamino)-desoxybenzoin (XVIBa) at 160° with a trace of acid actually did give the dehydromorpholine (dihydro-1,4-oxazine) (XIX) which was readily hydrolyzed by dilute aqueous acid to regenerate the original compound.



XIX

Further work is in progress in respect to other kinds of evidence dealing with these phenomena,[24] and in exploration of the influence of various structural factors and substituents in this and other series on the tendency to cyclize and on the stability of the cyclic forms.

Products of the Mannich Reaction.—A few Mannich-reaction products were made for comparison with respect to possible tumor-necrotizing activity (see experimental part). One of these of particular interest is the piperidyl hydroxyketone (XX) which was made from benzoin.



XX

There are analogies for this reaction in the Mannich reaction on tartronic acid[25] and in the condensation between formaldehyde and benzoin.[26]

Acknowledgment.—The preparation of the piperidyl alcohol-A (II) was first carried out by Dr. M. T. Clark.

Experimental[27]

The Preparation of the Secondary-Amino Desoxybenzoins (V) (Method 1).—(*cf.* Refs. 8). A mixture of 0.2 mole of benzoin, 0.22 mole of the appropriate amine and 2 g. of phosphorus pentoxide was heated on a water-bath for two to ten hours. The sirupy mixture was cooled, treated with water, stirred until crystallization of the base occurred, and filtered.

The hydrochlorides were prepared in one of the following ways: by dissolving the moist filter-cake in (a) ether or (b) an ether–acetone mixture, and adding ethereal hydrogen chloride; or (c) by triturating the moist filter-cake with dilute hydrochloric acid until the yellow color associated with the free base disappeared, followed by filtering, washing with hot water and then with acetone, and recrystallizing.

(d) In two preparations 2 ml. of concentrated hydrochloric acid was used as the catalyst instead of phosphorus pentoxide. The hydrochloride was precipitated as a resin by means of ethereal hydrogen chloride, digested with water and crystallized. Significant amounts of benzil were recovered from the mother liquors.

(e) In one preparation using diethylaminopropylamine, the reaction mixture (heated for two hours) was dissolved in ether. After washing with 10% sodium hydroxide and then with water, and after drying over sodium sulfate, the amino ketone was obtained as a clear yellow oil which resisted attempts to obtain a crystalline form; it was reduced successfully without purification and was readily hydrolyzed to benzoin by moist ethereal hydrogen chloride.

Preparation of the Tertiary-Amino Ketones (VIII) from Desyl Chloride (VII) (Method 2).—A mixture of desyl chloride and three equivalents of the secondary amine was heated at 60–65°. The resulting brown sirupy product was dissolved in ether and the solution was washed with water and dried over sodium sulfate. The hydrochloride was precipitated by addition of ethereal hydrogen chloride. In the case of the di-(β-ethanol)-amino compound, the crude product was washed with water, digested with a small amount of cold ether and crystallized as the base.

α-Piperidyldesoxybenzoin, which had been obtained previously in low yield by Rabe,[10] has now been made by allowing 0.5 mole of desyl chloride to react in ether solution with 1.5 moles of piperidine (twenty-four hours at room temperature). The precipitated piperidine hydrochloride was filtered and the ether evaporated. The crude yellow product was not pure after repeated crystallizations and though nearly colorless it gave low yields of the amino alcohol upon reduction. Purification was effected by washing several times with water, dissolving in 2 l. of 0.5 *N* hydrochloric acid, filtering from an orange-colored residue, extracting by a small amount of benzene, and neutralizing carefully with ammonium hydroxide. It crystallized as white fibrous needles of m. p. 82–83° (Rabe,[10] 82°).

Preparation of Amino Alcohols (IX) by Reduction of the Amino Ketones (Method 1).—A solution of the amino ketone hydrochloride and four equivalents of 3 *N* aluminum isopropoxide in an excess of isopropanol was refluxed until the test for acetone in the distillate became negligible. The excess solvent was distilled under reduced pressure and the residue was treated with an excess of 30% sodium hydroxide, and then with water. The precipitated, crude amino alcohol was filtered, washed, dried and recrystallized. (a) In one case the oily diethylaminopropylamino alcohol was taken up in ether, dried over sodium sulfate and precipitated as the dihydrochloride by ethereal hydrogen chloride; the base was then liberated by means of ammonium hydroxide and was recrystallized. (b) In another case, the oily morpholinyl derivative was precipitated as the hydrochloride from benzene by means of ethereal hydrogen chloride.

The 1,2-Diphenyl-2-piperidylethanols-A and B. (II) Reduction of α-Piperidyldesoxybenzoin.—A solution of 67 g. (0.24 mole) of purified α-piperidyldesoxybenzoin in 400 ml. of 1.8 *N* aluminum isopropoxide was refluxed for 6.5 hours and evaporated to a volume of about 100 ml. under reduced pressure. The viscous residue was hydrolyzed by shaking for one hour with 240 ml. of 4 *N* sodium hydroxide. Extraction with ether, washing, drying over sodium sulfate, and evaporation of the ether, gave a solid which was digested with cold ethanol; yield 59 g.; m. p. 79–81°. Crystallizations from ethanol raised the melting point of this mixture only slightly. It was dissolved in acetone and converted into the hydrochlorides by addition of ethereal hydrogen chloride. Crystallization of this mixture (51 g.) from 95% ethanol gave 20 g. (30%) of pure isomer-A hydrochloride; m. p. 260° (*in vacuo*); it was shown by mixture melting point to be identical with the compound obtained from *trans* stilbene oxide. The mother liquor upon evaporating to crystallization gave 19 g. of solid isomer-B hydrochloride (m. p. 202–203°) which was converted into the base by means of ammonium hydroxide. This base was recrystallized from ethanol; 18 g. (27%); m. p. 101–102°. It was identified by mixture melting point as the same isomer (B) that was obtained from *cis*-stilbene oxide.

Isomer-A ("erythro") methiodide was prepared by the action of methanolic methyl iodide at room temperature (twelve hours).

Isomer-A ("erythro") benzoate was prepared by shaking together 2 g. of the amino alcohol, 2.9 g. of benzoyl chloride and 10 ml. of 20% sodium hydroxide. The viscous oil which separated soon solidified as the temperature rose to 60°. Recrystallization twice from ethanol gave 0.8 g. of m. p. 166.5–167°.

Isomer-B ("threo") benzoate was made by heating a mixture of the isomer-B (base) with a slight excess of benzoyl chloride (65°) for two minutes, adding dilute sodium carbonate, filtering and crystallizing from ethanol; m. p. 143–144°.

Catalytic hydrogenation of the amino ketone hydrochloride in 95% ethanol with platinum oxide catalyst was stopped after one molecule had been absorbed. The

(24) Lutz and Jordan, papers in preparation on the acetophenone analogs and nuclear-halogenated derivatives.

(25) Mannich and Bauroth, *Ber.*, **55**, 3504 (1922).

(26) (a) Langenbeck, *C. A.*, **39**, 278 (1945) [*Oel. u. Kohle*, **40**, 206 (1944)]; (b) Schauenstein and Stampfer, *Ber.*, **77**, 19 (1944).

(27) (a) All melting points are "corrected"; (b) microanalyses were performed by Miss Geraldine Alley and Mrs. Joyce Blume Caliga.

products included some unchanged amino ketone, a 30% yield of the amino alcohol, isomer-A, and a large amount of non-basic by-products which were not further investigated.

In a 100:22 by volume mixture of 95% ethanol and concd. hydrochloric acid, reduction did not occur.

The dibenzoyl derivative of 1,2-diphenyl-2,N-benzylaminoethanol was made from the base by the action of pyridine and benzoyl chloride for fifteen minutes at 80–90°.

Preparation of the Amino Alcohols from *cis* and *trans* Stilbene Oxides (Method 2).—A mixture of *cis*[28a] or *trans*[2b] stilbene oxide (XII–XI) and an excess (20% or more) of the appropriate primary or secondary amine, was refluxed for one to eight hours, or, if the boiling point of the amine was above 150°, the reaction temperature was maintained at this point to avoid the decomposition which resulted at higher temperatures. The product was purified in one of the following ways:

(a) If the amine used was water soluble the reaction mixture was taken up in alcohol-free ether. The ether solution was washed with water, dried over sodium sulfate, and treated with ethereal hydrogen chloride to obtain the salt.

(b) If the product crystallized from the reaction mixture upon cooling it was filtered and recrystallized. The hydrochloride could then be obtained in the usual way.

(c) If the amine was water insoluble and the product did not crystallize directly on cooling, the mixture was taken up in ether and the unreacted amine was extracted with 1 *N* hydrochloric acid in which the reaction product was relatively insoluble. The ether solution containing the suspended water-insoluble salt of the reaction product was shaken with 10% sodium carbonate and was dried over sodium sulfate, and the salt was regenerated by addition of ethereal hydrogen chloride.

Reductive amination of benzil with cyclohexylamine (Method 3) was carried out using a mixture of 0.1 g. of platinum oxide (pre-reduced in the solvent), 75 ml. of absolute ethanol, 11 g. (0.1 mole) of cyclohexylamine and 10 g. (0.052 mole) of benzil. These conditions approximated those employed by Manske and Johnson in the synthesis of ephedrine.[11] Hydrogenation at atmospheric pressure was complete in nine hours.

A similar reduction using benzoin instead of benzil gave only *meso* hydrobenzoin, and this in nearly quantitative yield.

Platinum-catalyzed hydrogenation of benzil in the presence of piperidine under the above conditions gave only *meso* hydrobenzoin.

Preparation of the 1,2-Diphenyl-2-aminoethanols[15] from the Stilbene Oxides.—A mixture of 15 g. (0.0765 mole) of *trans*-stilbene oxide (XI), 25 ml. of dioxane and 35 ml. of concentrated ammonium hydroxide was heated in a sealed tube at 120° for ten hours. On cooling, a white solid (isomer-A) separated; 15 g. (92%); m. p. 160–163°. The hydrochloride was obtained by dissolving the pure base in methanol and adding concentrated hydrochloric acid until acid to congo.

The preparation of the diastereoisomer (B) from *cis*-stilbene oxide (XII) was carried out similarly.

Attempts to reduce the N-substituted tertiary ethanolamino ketones (XVIa, b, c), carried out as follows, gave in each case only unchanged material which was recovered in good yield and identified. A mixture of the amino ketone (base) (and the hydrochloride also in the case of XVIa) in 0.7–0.8 *N* aluminum isopropoxide was heated at refluxing for seven to eight hours, and was worked up in the usual way as described above.

2,3-Diphenyl-5,6-dihydro-4-ethyl-1,4-oxazine (XIX).—Two grams of the amino ketone (XVIa) was heated at 120° for fifteen minutes. One drop of concentrated hydrochloric acid was added, and the yellow salt became orange-colored. The temperature was brought to 160° for five minutes. The product crystallized on cooling and was recrystallized from ethanol; yield 1.2 g.; m. p. 88–89°. After recrystallization it melted at 89–90°; a mixture with starting material melted at 75–84°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.42; H, 7.22; N, 5.33.

The hydrochloride was not obtained in crystalline form. When heated with dilute hydrochloric acid the amino ketone was regenerated.

1,2-Diphenyl-3-N-morpholinylpropanone Hydrobromide,[29] $C_6H_5COCH(C_6H_5)CH_2NC_4H_8O$.—A mixture of 30 g. (0.153 mole) of desoxybenzoin, 27 g. of morpholine hydrobromide and 9 g. of paraformaldehyde in 30 ml. of absolute ethanol was refluxed for seven hours. The amino ketone hydrobromide precipitated on cooling and was crystallized from absolute ethanol; 16 g. (28%); m. p. 182–183°.

Anal. Calcd. for $C_{19}H_{21}NO_2 \cdot HBr$: N, 3.72. Found: N, 3.69.

The **hydrochloride** (SN 2589) was made similarly, starting with morpholine hydrochloride, and was crystallized from absolute ethanol; yield 43%; m. p. 176–178°.

Anal. Calcd. for $C_{19}H_{21}NO_2 \cdot HCl$: N, 4.22. Found: N, 4.02.

1,2-Diphenyl-2-hydroxy-3-N-piperidylpropanone (XX) (REL 644).—A solution of 21.2 g. (0.1 mole) of benzoin, 11 g. (0.13 mole) of piperidine, 11 g. (0.13 mole) of 35% formaldehyde in 75 ml. of ethanol was refluxed for seventy hours. (After two hours of heating an additional 5 g. of formaldehyde solution was added.) Cooling, filtering the precipitate and crystallization from ethanol gave 16.8 g. (55%); m. p. 68–69°. Recrystallizations did not raise the melting point.

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.37; H, 7.43; N, 4.50.

The **hydrochloride** was precipitated from acetone by ethereal hydrogen chloride (slow crystallization); m. p. 178–180° (*in vacuo*).

Anal. Calcd. for $C_{20}H_{23}NO_2 \cdot HCl$: C, 69.45; H, 6.99; N, 4.05. Found: C, 69.35; H, 6.84; N, 4.14.

Summary

Seven aliphatic α-secondary amino and the *p*-diethylaminoanilino desoxybenzoins have been made through the Voigt reaction by acid catalyzed condensation of benzoin with the appropriate primary amines. Three tertiary α-(β-hydroxyethylamino)-desoxybenzoins were made by condensing desyl chloride with the appropriate secondary amines.

Reductions of each of eight secondary and tertiary-aminodesoxybenzoins by means of aluminum isopropoxide gave one type (type-A) of amino alcohol except α-piperidyldesoxybenzoin which gave both of the two possible diastereoisomeric amino alcohols.

Six of the type-A amino alcohols including the parent aminohydrin itself, and also the compound obtained by reductive amination of benzil with cyclohexylamine, were obtained by condensation of *trans* stilbene oxide with the appropriate amines and ammonia, and four type-B stereoisomers, including the second isomer obtained in the reduction of α-piperidyldesoxybenzoin, were made similarly from *cis* stilbene oxide. The stereochemical mode of these reactions appears to be consistent.

(28) (a) Prepared according to Taylor and Crawford [*J. Chem. Soc.*, 1130 (1934)]; (b) prepared according to Tiffeneau and Levy [*Bull. soc. chim.*, **39**, 763 (1926)].

(29) *Cf.* piperidyl analog, Mannich and Lammering, *Ber.*, **55**, 3510 (1922).

The configurations of the amino alcohols have tentatively been assigned on the basis of the synthetic relation to the *cis* and *trans* stilbene oxides, assuming consistent *trans* reactions.

Because of the failure of α-(N-ethyl-N-ethanolamino)-desoxybenzoin and two related tertiary-nitrogen analogs to undergo reduction by aluminum isopropoxide, a cyclic structure for this type is suggested. Dehydration of one of these compounds was brought about by heating at 160°, and the reverse reaction was accomplished by the action of acid.

α-(Ethanolamino)-desoxybenzoin, in which the nitrogen is secondary, is reduced by aluminum isopropoxide and appears to be normal in its properties.

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[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Some Fluorinated Derivatives of Propane[1]

BY E. T. MCBEE, ANTHONY TRUCHAN AND R. O. BOLT[2]

This paper is one of a series[3] describing the synthesis of derivatives of fluoroalkanes; it offers an improved synthesis of $CF_3CH_2CF_3$ and describes new chlorofluoropropanes.

Hexachloropropene was subjected to the sequence

$$CCl_3CCl{=}CCl_2 \xrightarrow{SbF_3} CF_3CCl{=}CCl_2^{4} \xrightarrow{HF/SbCl_5} CF_3CHClCClF_2 \xrightarrow{Zn/C_2H_5OH} CF_3CH{=}CF_2 \xrightarrow{HF} CF_3CH_2CF_3^{5}$$

No addition of hydrogen fluoride across the double bond or halide replacement occurred when $CF_3CCl{=}CCl_2$ was heated with anhydrous hydrogen fluoride at 240° in a pressure vessel, but in the presence of antimony(V) halides reaction did occur. Rectification of the product showed that $CF_3CCl{=}CCl_2$, $CF_3CHClCCl_2F$, $CF_3CHClCClF_2$, $CF_3CHClCF_3$, $CF_3CCl_2CCl_2F$ and $CF_3CCl_2CClF_2$ were present in the mixture. Two independent reactions may be viewed as taking place, (a) addition of hydrogen fluoride to the double bond followed by halogen exchange and (b) addition of chlorine (from antimony (V) chlorofluorides) to the double bond followed by halogen exchange. $CF_3CHClCCl_2F$ was formed but it could not be rectified from unreacted $CF_3CCl{=}CCl_2$ because the difference in boiling points is only one degree. For physical constants, $CF_3CHClCCl_2F$ was independently prepared by fluorination of $CF_3CHClCCl_3$, obtained by addition of chlorine to $CF_3CH{=}CCl_2$. The structure of $CF_3CHClCClF_2$ was established by dechlorination to $CF_3CH{=}CF_2$,[4] and dehydrochlorination to $CF_3CCl{=}CF_2$.[3]

The ratio of $CF_3CHClCClF_2$ to $CF_3CHClCF_3$ was controlled by varying the amount of hydrogen fluoride used. The use of a 100% excess of hydrogen fluoride gave high yields of $CF_3CHClCF_3$ with a corresponding decrease in the yield of $CF_3CHClCClF_2$. The amount of $CF_3CCl_2CCl_2F$ and $CF_3CCl_2CClF_2$ varied with the amount of antimony(V) chloride used. Further fluorination of $CF_3CHClCF_3$ with anhydrous hydrogen fluoride and antimony(V) chloride did not take place even at temperatures of 260°. The starting material was recovered.

Bromine was added to $CF_3CH{=}CF_2$ under pressure at 140° to give $CF_3CHBrCBrF_2$. Hydrogen bromide was eliminated readily from the latter compound to give $CF_3CBr{=}CF_2$.

Experimental

Starting Materials and Apparatus.—The $CF_3CCl{=}CCl_2$ used in this work was prepared by the method of Henne and co-workers[4] from hexachloropropene (Hooker Electrochemical Company). J. T. Baker, C. P. antimony(V) chloride and anhydrous hydrogen fluoride (prime commercial grade from Harshaw) were used for the fluorinations.

Fluorination of $CF_3CCl{=}CCl_2$.—A 2-liter, nickel-lined autoclave was assembled, evacuated and then chilled to 0°. $CF_3CCl{=}CCl_2$ (3.25 moles), antimony(V) chloride (0.3 mole) and hydrogen fluoride (18.4 moles) were sucked into the autoclave in the order mentioned through the needle valve. The charged autoclave was heated in a stationary, vertical position for one hundred hours at 250 ± 5°. After cooling to 150°, the contents were released through the needle valve into a recovery train consisting of a gallon bottle three-fourths full of water, drying tower and, finally, a receiver cooled with solid carbon dioxide. No alkali was used in the water scrubber because $CF_3CHClCClF_2$ is easily dehydrochlorinated to $CF_3CCl{=}CF_2$. The organic product was steam distilled, dried and rectified in a suitable column. The products from three similar runs were combined for rectification. Purification of the compounds for chemical analysis and determination of physical properties was accomplished by washing with water, drying and re-rectifying. The recovery of $CF_3CCl{=}CCl_2$ plus an unknown amount of $CF_3CHClCCl_2F$ was 21%. The conversions to $CF_3CHClCF_3$, $CF_3CHClCClF_2$, $CF_3CCl_2CClF_2$ and $CF_3CCl_2CCl_2F$ were 16%, 50%, 2% and 2%, respectively.

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(3) E. T. McBee and co-workers, THIS JOURNAL, **62**, 3340–3341 (1940); **69**, 944–947 (1947); *Ind. Eng. Chem.*, **39**, 409, 418, 420 (1947).

(4) A. L. Henne, A. M. Whaley and J. K. Stevenson, THIS JOURNAL, **63**, 3478–3479 (1941).

(5) A. L. Henne and T. P. Waalkes, *ibid.*, **68**, 496–497 (1946).